

Metastasis of melanoma in non-sentinel nodes in patients with metastatic sentinel node. Can we avoid complementary lymphadenectomy?

Metástasis de melanoma en ganglios no centinela en pacientes con ganglio centinela metastásico. ¿Podemos evitar la linfadenectomía complementaria?

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Abstract

Background: Lymphatic mapping with sentinel node biopsy is the standard procedure for nodal staging in patients with cutaneous melanoma with a tumor thickness of 1 mm or greater. Patients who have metastases in it should undergo complementary lymphadenectomy; however, it has not been shown to improve survival. **Objective:** To know the prevalence in our environment of metastasis in the product of complementary lymphadenectomy in patients with metastatic sentinel node. **Method:** Evaluation of a descriptive, retrospective, observational, and analytical cohort of patients with metastatic sentinel nodes undergoing lymphadenectomy, with multivariate analysis of tumor thickness, neural invasion, location, number of sentinel nodes, serum lactate dehydrogenase concentration, lymph nodes dissected in lymphadenectomy, and rupture capsular. **Results:** There were 67 patients (35 women and 32 men), with a mean age of 66 years, in 22% there were metastases in lymph nodes from complementary lymphadenectomy and in 19% capsular rupture; unrelated to the Breslow level. Capsular rupture in the sentinel node, lymphadenectomy time, and perineural invasion were prognostic factors for metastasis in non-sentinel nodes. **Conclusions:** In this series, 22% of the patients had metastases in non-sentinel lymph nodes, 19% of them with capsular rupture, which justifies complementary lymphadenectomy.

Keywords: Sentinel node. Biopsy. Cutaneous melanoma. Lymphadenectomy.

Resumen

Antecedentes: El mapeo linfático con biopsia del ganglio centinela es el procedimiento estándar de estadificación ganglionar en pacientes con melanoma cutáneo con grosor tumoral de 1 mm o mayor. Los pacientes que tienen metástasis en él deben ser sometidos a linfadenectomía complementaria; sin embargo, esta no ha mostrado mejorar la supervivencia. **Objetivo:** Conocer la prevalencia en nuestro medio de metástasis en el producto de linfadenectomía complementaria en pacientes con ganglio centinela metastásico. **Método:** Evaluación de una cohorte descriptiva, retrospectiva, observacional y analítica de pacientes con ganglio centinela metastásico sometidos a linfadenectomía, con análisis multivariado de grosor tumoral, invasión neural, localización, número de ganglios centinela, concentración sérica de deshidrogenasa láctica, ganglios disecados en linfadenectomía y ruptura capsular. **Resultados:** Hubo 67 pacientes (35 mujeres y 32 hombres), con una media de 66 años de edad, en el 22%

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hubo metástasis en ganglios de linfadenectomía complementaria y en el 19% ruptura capsular; sin relación con el nivel de Breslow. La ruptura capsular en el ganglio centinela, el tiempo de linfadenectomía y la invasión perineural fueron factores pronóstico de metástasis en ganglios no centinela. **Conclusiones:** En esta serie, el 22% de los pacientes tuvieron metástasis en ganglios no centinela, el 19% de ellos con ruptura capsular, lo cual justifica la linfadenectomía complementaria.

Palabras clave: Ganglio centinela. Biopsia. Melanoma cutáneo. Linfadenectomía.

Introduction

For many years it was debated whether performing elective lymphadenectomy in patients with cutaneous melanoma (without lymph node metastases) was useful or not. The discussion focused on the poor oncological usefulness and the high rate of complications¹, as up to 45% of patients who underwent lymphadenectomy had postoperative complications, mainly lymphedema.

The discussion never ended and it was not until 1992², when validating the technique of lymphatic mapping with sentinel node biopsy (MLBGC), when it was possible to identify patients who were candidates for the procedure in whom morbidity was justified.

The MLBGC allows us to identify the first lymph node relay, the one with the highest risk of having metastasis, and depending on its histological status, we can decide whether it is necessary to perform lymphadenectomy or not. Patients with sentinel lymph node (SLN) without metastases can be monitored, and those with metastases in the SLN should undergo complementary lymphadenectomy (LC) in a second stage.

The MLBGC made it possible to reach a consensus between those who proposed elective or prophylactic dissection and those who indicated it therapeutically (in the face of lymph node relapse). However, it is currently being debated whether all patients who have metastases in the SLN should undergo LC or not, since systematic LC does not necessarily improve survival, but it does imply greater morbidity.

It has recently been shown that CL in patients with metastatic SLN does not improve overall survival, although it does increase regional control, but on the other hand, patients who undergo it have greater morbidity than those who are observed³.

Around 11.5% of patients with metastases in the SLN have metastases in the non-sentinel lymph nodes (NCN), although this frequency varies in the literature and can reach up to 66%⁴. These patients, at some point during their follow-up, will require therapeutic lymphadenectomy due to lymph node relapse

in the previously mapped area, which, although it probably does not impair survival, does increase the rate of complications when compared with CL at the time of diagnosis of metastasis in the SLN³.

The recent advent of adjuvant therapy with nivolumab in stage 3 patients requires adequate lymph node staging, which makes the role of LC in patients with metastatic GC even more debatable⁴.

The aim of this study is to determine the characteristics of the NCN in patients who underwent SLNM with the combined technique and who had cutaneous melanoma metastases in the SLN, which would eventually be candidates for LC.

Method

Descriptive, retrospective, observational and analytical cohort of patients diagnosed with cutaneous melanoma who underwent SLNM and the SLN was positive for malignancy due to the presence of metastasis, and therefore underwent complementary lymph node dissection of the lymphobearing area. Data from clinical records were collected. The statistical analysis was analytical.

The primary aim was to determine the prevalence of CNG metastases in LC. The clinicopathological characteristics of the lymph node dissection products in these patients are described, as well as the clinicopathological characteristics of the primary tumor and of the SLNs obtained by lymphatic mapping in these patients.

The variables evaluated were the type of melanoma, the stage (pT) and the location, the number of SLNs obtained, the number of metastatic nodes, the presence of capsular rupture in the SLN, comorbidity and serum concentrations of lactic dehydrogenase (LDH). In the LC, the number of dissected lymph nodes, the number of metastatic lymph nodes and the presence or absence of lymph node capsular rupture were evaluated.

Sample size calculation was performed using the statistical package StatCalc Statistical, assuming a prevalence of positive nodal disease of 11.5% with a

power of 80% or beta, and an alpha of 0.05%. This resulted in 67 patients to be evaluated.

The study followed all the indicated recommendations and ethical standards, as well as the regulations of the General Health Law on Research for Health and the Declaration of Helsinki of 1975 and its amendments, as well as current international codes and standards for good clinical research practice. The principles contained in the Nuremberg Code, the Declaration of Helsinki and its amendment, the Belmont Report and the United States Code of Federal Regulations were fully respected.

The study was carried out with the institution's resources, without implying expenses added to those usually required by the population to be studied, in this case patients with a diagnosis of cutaneous melanoma, requiring the collection and analysis of clinical and histopathological data systematically determined in this population.

Results

319 records of patients diagnosed with cutaneous melanoma were evaluated, obtaining 67 cases that met the selection criteria. In all of them, the SLN obtained by the lymphatic mapping technique with the combined technique (rhenium colloid and patent blue V) presented melanoma metastases, and all underwent LC of the area subjected to mapping.

The distribution by sex was 32 men (47.7%) and 35 (52.3%) women, and the mean age was 66.07 years, with a range of 42 to 85 years.

There were 26 patients (38.80%) with diabetes mellitus and 30 (44.77%) diagnosed with systemic arterial hypertension.

Preoperative DHL was determined in 42 patients (62.68%) and the mean figure was 192.59 U/dl, with a range of 92 to 472 U/dl. Patients with negative LC for metastasis had a mean serum LDH of 181.2 U/dl, with a range of 92 to 385 U/dl, while those with lymph node metastases in the LC had a mean figure of 229.88 U/dl, with a range of 124 to 472 U/dl.

The mean number of SLNs dissected was 1.8, with a range of 1 to 8 nodes. The mean number of CNG dissected in the LC was 12.6, with a range of 5 to 35.

Of the 67 patients who underwent CL, 15 (22.38%) had metastases in at least one CNG in the lymphadenectomy specimen, with a range of 1 to 12 nodes with melanoma metastases.

Capsular rupture was identified in 19.40% of the patients with metastases in the CNG, and this percentage

was higher (23%) in patients with localization of melanoma in the lower extremities.

Patients with lymph node metastases in the LC had a mean serum DHL of 229.88 U/dl, compared to 181.2 U/dl in patients with negative lymphadenectomy.

In the multivariate analysis, the factors that predicted the presence of metastasis in the CNG were the capsular rupture of the sentinel node ($p < 0.001$), the time elapsed between the MLBGC and the LC (> 12 months) and perineural infiltration in the primary tumor ($p = 0.009$).

We found no difference in terms of Breslow, but the distribution of tumor thickness was not homogeneous and 80% of our patients had a tumor thickness > 2 mm.

Discussion

MLBGC with combined technique is the standard for lymph node staging in patients with cutaneous melanoma with tumor thicknesses of 1 mm or more^{5,6}. The SLN offers prognostic information and identifies patients at higher risk of having occult metastases in the CNG, in whom the possibility of performing lymphadenectomy should be considered.

The MLBGC reduces the morbidity of systematic dissection by identifying which patients are not candidates for this surgical procedure in a systematic way^{7,8}.

Patients with metastatic SLN have a higher risk of having hidden metastases. In this series, 22.3% of the patients with metastases in the SLN had metastases in the SLN, and 19% had capsular rupture, which is an adverse prognostic factor for lymph node relapse. The LC in these patients allowed their identification.

CL in patients with metastatic SLN has not shown any improvement. Pray melanoma-specific survival in the two largest randomized trials: MSLT II and DeCOG-SLT^{9,10}. However, in both studies regional control is better in patients undergoing CL than in those observed.

It is important to mention that both studies show weaknesses. In the MSLT-II, the follow-up is 43 months, 38% of the patients did not accept randomization and only 30% of them had SLN with metastases > 1 mm. On the other hand, in the DeCOG-SLT trial, follow-up was 35 months, recruitment was much lower than expected (which makes the trial less powerful), 60% of patients had SLN metastases of 1 mm or less. (which implies a much lower possibility of metastasis in the CNG and consequently a lower stage), patients with melanoma located in the head and neck were

excluded, and 60% of the patients received treatment with adjuvant interferon (which delays the nodal relapse and could make the 35 months of follow-up too short to be able to conclude an adequate evaluation, and the long-term results could change).

Despite this, it is currently considered that CL is not the standard of care in patients with melanoma metastases in the SLN, and that observation is an appropriate alternative as long as it is close every 3 months in the first 2 years, both clinically and by high-resolution ultrasound⁵.

In our own experience and in our population, which presents greater tumor thickness and a greater metastatic tumor burden in the SLN, we observed that more than 20% of patients have metastases in the other lymph nodes in the lymph node area when the SLN has metastasis and almost 20% of them have lymph node capsular rupture, which is an adverse prognostic factor for regional relapse, so we consider that we do not have sufficient evidence to ignore CL in these patients.

Although in the present study we did not find a difference in the metastases in the CNG in relation to the Breslow, since the majority of our patients have thicknesses > 2mm, perhaps, according to the results of the literature, patients with intermediate thicknesses (between 1 and 2 mm) and with microscopic metastases in the SLN could be candidates for follow-up in our environment whenever possible.

The lack of evidence of positive SLN follow-up in patients with melanoma located in the head and neck leads us to suggest that all patients with these characteristics should undergo parotidectomy or modified radical neck dissection, or both, depending on the location of the primary tumor.

Conclusions

The histological state of the SLN in patients with cutaneous melanoma is the most important prognostic factor and in the present series it is associated with 22% of metastases in the SLN, 19% of them with capsular rupture, which allows us to conclude that all A patient with melanoma metastases in the SLN should undergo LC. This allows us to offer better

regional control and select high-risk patients who are candidates for adjuvant therapies, whether regional (radiotherapy) or systemic.

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Conflicts of interest

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Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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